April 9, 2015

**New Longer-Term IMBRUVICA® (ibrutinib) Data Show High Response Rates in Patients with Waldenstrom’s Macroglobulinemia**

**Data Published in The New England Journal of Medicine Show 91% Overall Response Rate and 95% Overall Survival**

SUNNYVALE, Calif., April 9, 2015 /PRNewswire/ -- Pharmacyclics, Inc. (NASDAQ: PCYC) today announced longer-term data from a Phase II investigator-initiated study showing Waldenstrom's macroglobulinemia (WM) patients treated with IMBRUVICA® (ibrutinib) experienced sustained disease control with an overall response rate (ORR) of 91% after a median of 19.1 months of treatment and a 2-year overall survival (OS) rate of 95%. These updated results were published last night online in *The New England Journal of Medicine* (NEJM). An earlier analysis of the data served as the basis for the January 2015 U.S. Food and Drug Administration approval of IMBRUVICA for the treatment of all patients with WM. IMBRUVICA is jointly developed and commercialized by Pharmacyclics and Janssen Biotech, Inc.

"The results are remarkable when you consider that patients had received an average of two prior therapies, and 40% showed no response to the previous treatments," said lead investigator Steven P. Treon, M.D., Ph.D., Director of the Bing Center for Waldenstrom's Macroglobulinemia at the Dana-Farber Cancer Institute and Associate Professor at Harvard Medical School, Boston, Mass. "The findings herald a new era for the treatment of Waldenstrom's macroglobulinemia."

The Phase II, prospective, open-label, multi-center study evaluated the safety and tolerability of IMBRUVICA 420 mg orally, once daily until disease progression or unacceptable toxicity in 63 previously treated patients who had received a median of two prior therapies (range 1-9). The primary endpoint was ORR, which was defined as a sum of minor (MR), partial (PR), very good partial (VGPR) and complete responses (CR), as well as major (PR+VGPR+CR) response rates as assessed by investigators and an independent review committee (IRC) using criteria adopted from the International Workshop of Waldenstrom’s Macroglobulinemia. Secondary endpoints included progression-free survival (PFS) and safety. Fifty-six of the 63 patients (89%) were found to express the MYD88L265P mutation and 21 patients (34%) had the CXCR4<sup>WT</sup> mutation. These mutations promote the growth and survival of WM cells and have emerged as new targets for the treatment of patients with WM.¹

After a median treatment duration of 19.1 months (range 0.5-29.7), IMBRUVICA was associated with a 91% ORR. Estimated PFS and OS rates at 24 months (secondary endpoints) were 69% (95% CI, 53.2-80.5%) and 95.2% (95% CI, 86.0-98.4), respectively. Notably, IMBRUVICA was also associated with a rapid onset of response, with a median time to response of four weeks. Investigator-determined responses were impacted by the MYD88 and CXCR4 mutations; patients carrying MYD88<sup>L265P</sup> and CXCR4<sup>WT</sup> achieved the highest responses, with a 100% ORR and 91% major response rate. Overall, IMBRUVICA was well tolerated and there were no unexpected toxicities. At the time of analysis, 43 patients (68%) remained on therapy.

"The strength of these results are compelling, as they reinforce earlier data on which IMBRUVICA was approved for Waldenstrom's macroglobulinemia and show even greater efficacy in difficult-to-treat patients," said Thorsten Graef, M.D., Ph.D., Head of Hematology and Global Medical Safety at Pharmacyclics.

The most common Grade 2-4 adverse events (AEs; occurring in >10% of all patients) associated with IMBRUVICA were neutropenia (22.2%) and thrombocytopenia (14.3%). Grade 3 neutropenia and thrombocytopenia occurred in nine (14.3%) and eight (12.7%) patients, respectively. Of note, IMBRUVICA-related neutropenia and thrombocytopenia were reversible, but required a reduction in dose and/or discontinuation of treatment with IMBRUVICA in three of the four patients who developed these conditions. Grade 2 bleeding events occurred in four patients and there were few infections potentially attributed to IMBRUVICA. Atrial fibrillation (AFib) related to IMBRUVICA occurred in three patients, all of whom had a prior history of paroxysmal AFib. AFib resolved when IMBRUVICA was withheld and all three patients were able to continue on therapy per protocol without further event.

Treatment discontinuation remained low (31%) and was consistent with the rates observed in the earlier analysis.

**About Waldenstrom's Macroglobulinemia**

Waldenstrom's macroglobulinemia (WM; a clinically recognized subset of lymphoplasmacytic lymphoma, or LPL) is a slow-growing and rare blood cancer that most commonly originates from B cells, a type of white blood cell (lymphocyte) that develops in the bone marrow.² In the United States, approximately 1,000 to 1,500 people are diagnosed each year,³ with the median age
at diagnosis being 60 to 70 years of age. WM occurs as the result of a malfunction in the healthy lifecycle of a B cell, causing the cell to become malignant and reproduce at an abnormal rate. The malignant B cells produce large amounts of an abnormal type of antibody protein called immunoglobulin M (IgM). Excess IgM causes the blood to thicken and causes many of the symptoms of WM.

About IMBRUVICA
IMBRUVICA (ibrutinib) is a first-in-class, oral, once-daily therapy that inhibits a protein called Bruton's tyrosine kinase (BTK). BTK is a key signaling molecule in the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B cells. IMBRUVICA blocks signals that tell malignant B cells to multiply and spread uncontrollably.

IMBRUVICA is approved for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, CLL patients with del 17p, a genetic mutation that occurs when part of chromosome 17 has been lost, and patients with Waldenstrom's macroglobulinemia.

IMBRUVICA is also approved for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Accelerated approval was granted for the MCL indication based on overall response rate (ORR). Continued approval for the MCL indication may be contingent upon verification of clinical benefit in confirmatory trials.

IMBRUVICA is being studied alone and in combination with other treatments in several blood cancers. Over 5,100 patients have been treated in clinical trials of IMBRUVICA conducted in 35 countries by more than 800 investigators. Currently, 13 Phase III trials have been initiated with IMBRUVICA and 58 trials are registered on www.clinicaltrials.gov.

IMBRUVICA was one of the first medicines to receive U.S. FDA approval via the new Breakthrough Therapy Designation pathway, and is the only product to have received three Breakthrough Therapy Designations.

To learn more about the medical terminology used in this news release, please visit http://stedmansonline.com/.

INDICATIONS
IMBRUVICA is indicated to treat people with:

- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- Chronic lymphocytic leukemia (CLL) with 17p deletion
- Waldenstrom's macroglobulinemia
- Mantle cell lymphoma (MCL) who have received at least one prior therapy - accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Patients taking IMBRUVICA for CLL or WM should take 420 mg taken orally once daily (or three 140 mg capsules once daily).

Patients taking IMBRUVICA for MCL should take 560 mg taken orally once daily (or four 140 mg capsules once daily).

Capsules should be taken orally with a glass of water. Capsules should be taken whole. Do not open, break, split or chew the capsules.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and non-fatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with
IMBRUVICA®. Monitor patients for fever and infections and evaluate promptly.

**Cytopenias** - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA®. Monitor complete blood counts monthly.

**Atrial Fibrillation** - Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA® treatment and dose modification.

**Second Primary Malignancies** - Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11%).

**Tumor Lysis Syndrome** - Tumor lysis syndrome has been reported with IMBRUVICA® therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

**Embryo-Fetal Toxicity** - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA®. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

**ADVERSE REACTIONS**

The most common adverse reactions (>25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash. Seven percent of patients receiving IMBRUVICA® discontinued treatment due to adverse events.

**DRUG INTERACTIONS**

**CYP3A Inhibitors** - Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

**CYP3A Inducers** - Avoid co-administration with strong CYP3A inducers.

**SPECIFIC POPULATIONS**

**Hepatic Impairment** - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

For additional important safety information, please see Full Prescribing Information at [http://www.imbruvica.com/downloads/Prescribing_Information.pdf](http://www.imbruvica.com/downloads/Prescribing_Information.pdf).

**About Pharmacyclics**

Pharmacyclics, Inc. (NASDAQ: PCYC) is a biopharmaceutical company focused on developing and commercializing innovative small-molecule drugs for the treatment of cancer and immune mediated diseases. The company's mission is to build a viable biopharmaceutical company that designs, develops and commercializes novel therapies intended to improve quality of life, increase duration of life and resolve serious unmet medical needs. It will do so by identifying and controlling promising product candidates based on scientific development and administrative expertise, developing its products in a rapid, cost-efficient manner and, pursuing commercialization and/or development partners when and where appropriate.

Pharmacyclics markets IMBRUVICA and has three product candidates in clinical development and several preclinical molecules in lead optimization. The company is committed to high standards of ethics, scientific rigor and operational efficiency as it moves each of these programs to commercialization. Pharmacyclics is headquartered in Sunnyvale, CA. To learn more, please visit [www.pharmacyclics.com](http://www.pharmacyclics.com).

**NOTE:** This announcement may contain forward-looking statements made in reliance upon the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended,
including statements, among others, relating to our future capital requirements, including our expected liquidity position and timing of the receipt of certain milestone payments, and the sufficiency of our current assets to meet these requirements, our future results of operations, our expectations for and timing of ongoing or future clinical trials and regulatory approvals for any of our product candidates, and our plans, objectives, expectations and intentions. Because these statements apply to future events, they are subject to risks and uncertainties. When used in this announcement, the words "anticipate", "believe", "estimate", "expect", "expectation", "goal", "should", "would", "project", "plan", "predict", "intend", "target" and similar expressions are intended to identify such forward-looking statements. These forward-looking statements are based on information currently available to us and are subject to a number of risks, uncertainties and other factors that could cause our actual results, performance, expected liquidity or achievements to differ materially from those projected in, or implied by, these forward-looking statements. Factors that may cause such a difference include, without limitation, our need for substantial additional financing and the availability and terms of any such financing, the safety and/or efficacy results of clinical trials of our product candidates, our failure to obtain regulatory approvals or comply with ongoing governmental regulation, our ability to commercialize, manufacture and achieve market acceptance of any of our product candidates, for which we rely heavily on collaboration with third parties, and our ability to protect and enforce our intellectual property rights and to operate without infringing upon the proprietary rights of third parties. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, performance or achievements and no assurance can be given that the actual results will be consistent with these forward-looking statements. For more information about the risks and uncertainties that may affect our results, please see the Risk Factors section of our filings with the Securities and Exchange Commission, including our Form 10-K for the year ended December 31, 2013 and quarterly reports on Form 10-Q. We do not intend to update any of the forward-looking statements after the date of this announcement to conform these statements to actual results, to changes in management's expectations or otherwise, except as may be required by law.

*Disclaimer: Dr. Treon served as principal investigator of this Dana-Farber Cancer Institute-sponsored clinical study. He has served as a paid advisor to both Pharmacyclics and Janssen in developing the compound ibrutinib. Dr. Treon does not have a financial interest in either company. The Dana-Farber Cancer Institute has received research funding from Pharmacyclics in conjunction with this clinical trial.

IMBRUVICA is a registered trademark of Pharmacyclics, Inc.

5 IMBRUVICA Prescribing Information, January 2015


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